EXHIBIT 7

Malformation in infants of mothers with epilepsy receiving antiepileptic drugs

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Article abstract—To assess the relative contribution of antiepileptic drugs (AEDs) to occurrence of congenital malformations, we compared two prospective studies. We analyzed data for 14 AEDs for total daily doses (drug score) and eight background factors. From the first study, the drug score and polytherapy—particularly the use of valproate plus carbamazepine—were suspected to be primary factors for increased incidence of congenital malformation. In the other study, the drug score for each case was decreased, and polytherapy—particularly valproate plus carbamazepine—was changed to monotherapy before conception. These changes significantly decreased the incidence of malformations. Among risk factors, only the doses of methylphenobarbital for mothers of infants with malformations were significantly higher than those for mothers of infants without malformations. Statistical differences were seen in drug score, number of AEDs, maternal age at delivery, seizure type, and etiology of epilepsy between the two groups. When data were corrected for seizure type, maternal age at delivery, or etiology of epilepsy, the difference in the incidence of malformations did not disappear, but it did disappear when data were corrected for drug score or number of AEDs. These results support our previous observations that AEDs are primary factors for the increased incidence of congenital malformation in infants of mothers with epilepsy.

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Improved diagnosis and therapy, together with better social adjustment, have allowed most women with epilepsy to marry and bear children. However, the incidence of congenital malformations among infants of mothers with epilepsy (IME) treated with antiepileptic drugs (AEDs) during pregnancy is higher than that among infants of normal controls[1,2] or among IME whose mothers were not treated with AEDs during pregnancy.[2-4] In recent prospective studies, teratogenicity appeared to be attributable to AEDs rather than to epilepsy.[5-7] Animal experiments also established that most AEDs have teratogenic effects.[8,9]

In our previous (1978 to 1984) prospective study of 172 AED-exposed IME[6] and 20 nonexposed IME,[5] high doses of AEDs and polytherapy (with valproic acid in particular) were found to be primary factors for the increased incidence of congenital malformations in IME treated with AEDs. Reduced folate levels in response to AED therapy also were related to the occurrence of malformations.[10,11] The involvement of other risk factors, however, such as environmental factors, maternal hypoxia,[12] and genetic influences,[13-16] also must be considered in the etiology of congenital malformations. The aim of the present (1985 to 1989) study was to evaluate the effects of AED-related factors, among many putative risk factors, on the incidence of congenital malformations in IME. In so doing, we hoped to compare two prospective study groups of IME in which the AED regimens used during pregnancy were different. Results of analysis in a total of 337 cases will be reported separately.

Subjects and methods. The present study group was selected prospectively from 1985 to 1989 and included 145 infants born to AED-treated mothers with epilepsy at Hirosaki University Hospital, Nagasaki University Hospital, Fukushima Medical College Hospital, and Nagoya National Hospital. A previous group was selected prospectively from 1978 to 1984 and included 172 infants of AED-treated mothers[6] and 20 infants of non-AED-treated mothers with epilepsy.[5] The mothers had no congenital anomalies. In each case of the mothers with epilepsy, seizures had started before conception.

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All mothers with epilepsy received AEDs during pregnancy except for two in the present study and 20 in the previous study.

In the older series, patients received AEDs in accordance with standard practice habits, and no attempt was made to change regimens. Whenever possible, patients in the present study were treated with one AED and changed from polytherapy to monotherapy before conception. The combination of valproate and carbamazepine was avoided. With this exception, the design of our present study[5] was exactly the same as that of the previous study.[6] All infants were examined in a systematic way, according to a standardized checklist based on the report of the Japanese Association of Obstetricians for Maternal Welfare.[17] Data on the following variables were recorded: maternal age at delivery; gravida; outcome of previous pregnancy; etiology of epilepsy; classification of epileptic seizures; occurrence of seizure during the first trimester of pregnancy; change in seizure frequency during pregnancy; and gender of offspring.

Fourteen AEDs and their drug score (table 1) also were recorded. The drug-scoring system was adopted to detect relationships between the effects of AEDs and the occurrence of malformation and was applied because some of the subjects had been treated with more than one AED.

The relationship between malformations and the variables and the difference in the incidence of malformations between the present and previous study groups were analyzed with the χ^2 test, Wilcoxon rank sum test, Mantel-Haenszel test, and Breslow-Day test. The χ^2 test was used for analysis of nominal data, and the Wilcoxon rank sum test was used for ordered category data. The Mantel-Haenszel test was used for comparisons of the incidence of malformations between our present series and previous series when the data were corrected for factors that differed significantly between the two studies. The Breslow-Day test was applied to confirm homogeneity of incidence among strata.

Results. Details concerning the observed malformations and drug combination patterns in the present subjects are shown in table 2. Nine (6.2%) of 145 IME treated with AEDs had major or minor malformations, consisting of cleft lip and heterotaxia, coloboma iridis, ventricular septal defect, spina bifida, cleft lip and palate, pilonidal sinus, right accessory auricle, deformity of the skull, and sacral nevus. No relationship existed between the type of defect and individual AEDs.

Among risk factors studied, only methylphenobarbital showed a significant association with malformations ($p = 0.014$). Two IME among a total of seven exposed to methylphenobarbital had malformations in our present study. Among a total of 337 women from both series, 20 were exposed to methylphenobarbital and five of their offspring had malformations. Among these five infants with malformations, only one was exposed to methylphenobarbital as monotherapy (one of three methylphenobarbital cases); four other malformed infants were exposed to methylphenobarbital in combination with phenytoin, with or without other AEDs. No significant association was seen between the presence of malformations and other putative risk factors.

Table 1. Drug-scoring system: amount of each of the primary anticonvulsant drugs constituting 1 unit in calculations of total and maximal daily dose

Drug	Amount of drug (mg/d)
Phenytoin	50
Phenobarbital	50
Primidone	100
Carbamazepine	100
Valproic acid	100
Ethosuximide	250
Sulthiame	50
Acetazolamide	125
Pheneturide	200
Diazepam	5
Nitrazepam	5
Methylphenobarbital	75
Clonazepam	1
Zonisamide	75

The incidence of malformations in the present study group (6.2%) was significantly lower ($p = 0.031$) than that reported in the previous study group (13.5%) (table 3). The incidence of malformations in these groups among infants exposed to AEDs was 6.3% and 14%, respectively, and the difference between the two was significant ($p = 0.030$). The mean ± SD) maternal age at delivery among patients in the previous and present studies was 26.54 ± 4.18 (18 to 46 years) and 27.37 ± 4.36 (18 to 40 years), respectively, and the difference was significant ($p = 0.0044$).

In the previous study group, 171 women (89.1%) had idiopathic epilepsy and 21 (10.9%) had symptomatic (organic) epilepsy, whereas in the present study, 143 (98.6%) had idiopathic epilepsy and two (1.4%) had symptomatic epilepsy. The difference between the previous and the present study groups with regard to etiology of epilepsy was significant ($p \fallingdotseq 0.00$).

The previous study group consisted of 103 patients (53.6%) with primary generalized seizures, 24 (12.5%) with secondarily generalized seizures, 22 (11.5%) with simple partial seizures, 28 (14.6%) with complex partial seizures, and 15 (7.8%) with mixed types of seizures. In the present study group, 62 (42.8%), 18 (12.4%), 8 (5.5%), 35 (24.1%), and 22 (15.2%) subjects had the respective seizure types. The difference between these two groups with regard to seizure types was significant ($p = 0.004$).

The number of mothers exposed to various AEDs

Table 2. Anomalies observed among infants of mothers treated with AEDs in the present study

Case	AED (mg/d)	Anomalies
1	CBZ (400)	Cleft lip, heterotaxia
2	CBZ (800)	Coloboma iridis
3	VPA (600)	Ventricular septal defect
4	VPA (1200)	Spina bifida aperta
5	PHT (280) MPB (100) PRM (600), VPA (600) Sulthiame (600)	Cleft lip and palate
6	PHT (210), PB (80) CBZ (400)	Pilonidal sinus
7	PHT (100) MPB (200)	Right accessory auricle
8	PHT (200), PRM (200) CBZ (500)	Deformity of skull
9	PHT (250), PB (80) CBZ (400)	Sacral nevus

AED = antiepileptic drugs. VPA = valproic acid. MPB = methylphenobarbital.
CBZ = carbamazepine. PHT = phenytoin. PRM = primidone.
PB = phenobarbital.

Table 3. Incidence of malformations among infants of mothers with epilepsy in the present and previous studies

	No. (%)			
	Previous study (N = 192)	Present study (N = 145)	Total (N = 337)	*p*
Major/minor malformations	26 (13.5)	9 (6.2)	35 (10.4)	
No malformations	166	136	302	0.031

and their drug scores are shown in table 4. Thirty-one mothers in the previous study group and 92 in the present study group received a single drug. The remaining patients received multiple drugs. The percentage of women receiving monotherapy increased from 16.1% in the previous study group to 63.4% in the present study group. The incidence of valproic acid therapy increased from 14.1 to 29.7%, and valproic acid monotherapy increased from 13 to 69%. Among 14 AEDs administered to mothers in the present study group, doses were significantly lower than those administered in the previous study group ($p < 0.05$), except for those of carbamazepine, ethosuximide, sulthiame, diazepam, nitrazepam, methylphenobarbital, clonazepam, and zonisamide. The dose of valproic acid was significantly higher in the present study group (mean ± SD of drug score, 2.08 ± 3.75) than in the previous study (0.95 ± 2.66) ($p = 0.001$). The drug score and number of AEDs administered to patients in the present study also were significantly lower than those in the the previous study (table 5).

The incidences of malformations associated with individual AEDs in the present study group were: 4.6% for phenytoin (3 of 65), 10% for phenobarbital (2 of 20), 0% for primidone (0 of 19), 7.3% for carbamazepine (4 of 55), 7% for valproic acid (3 of 43), and 28.6% for methylphenobarbital (2 of 7). The incidences in the previous study group were 14.6% for phenytoin (20 of 137), 9.9% for phenobarbital (7 of 71), 17.4% for primidone (16 of 92), 19.4% for carbamazepine (13 of 67), 25.9% for valproic acid (7 of 27), and 23.1% for methylphenobarbital (3 of 13). The incidence of malformations in infants exposed to methylphenobarbital was high in both studies. No definite dose-dependent increase in the incidence of malformations was associated with any particular AED in either study group, except for methylphenobarbital in the present study group.

Table 6 summarizes the results of comparisons of the incidence of malformations in the previous and present studies after correction for the five factors that differed significantly between the two studies. Even after correction for three variables—age at delivery, etiology of epilepsy, and classification of seizures—the significant difference in the

incidence of malformation did not disappear. After correction for maternal age at delivery, the p value by the Mantel-Haenszel test was 0.028; for etiology of epilepsy, $p = 0.032$; and for seizure type, the p value was 0.049. On the other hand, the significant difference in incidence disappeared after correction for drug score or number of AEDs.

Discussion. Although many reports on teratogenic effects of AEDs in animal studies have been published, no definite clinical evidence concerning teratogenicity and AEDs has been obtained. In the present study, analysis of possible risk factors with the Wilcoxon rank sum test revealed a significant association between methylphenobarbital exposure and congenital malformations. On the other hand, the drug score and exposure to valproic acid, both of which were significantly associated with malformations in the previous study group,[6] lost their significance in the present study group. This change might be attributable to the reduced number of women receiving valproic acid polytherapy, since the dose of valproic acid has increased in the present study group, compared with that used in the previous study group, and reduction in drug score also was causally related to the decreased incidence of malformations. No significant association was noted between the presence of malformations and the other putative risk factors.

Regarding the teratogenicity of methylphenobarbital, none has been reported to date. As usually supplied, methylphenobarbital is a racemic mix of R and S isomers. Kupfer and Branch[18] reported that the S isomer of methylphenobarbital was cleared mainly by demethylation, whereas the R isomer was eliminated rapidly by both aromatic hydroxylation and demethylation in subjects who metabolized the drug extensively, but only by demethylation in subjects who metabolized it poorly. The incidence of poor metabolism of methylphenobarbital is reported to be 18% in the Japanese population and 5% in Caucasians.[19]

Like primidone, phenytoin, and carbamazepine, methylphenobarbital forms epoxide intermediates.[20] Perhaps there are more poor metabolizers of methylphenobarbital among Japanese subjects than among Caucasians. Methylphenobarbital undergoes a polymorphic pattern of metabolism that appears to be coregulated with phenytoin derivatives such as mephenytoin.[21] Phenytoin and mephenytoin also share, to some extent, the same metabolic pathway,[22] indicating that coadministration of methylphenobarbital and phenytoin might result in increased levels of both. Most women in the present study who had malformed infants had been exposed to both methylphenobarbital and phenytoin (with or without other AEDs). Thus, levels of phenytoin and methylphenobarbital might increase, and teratogenic epoxide intermediates of both AEDs might accumulate. These possibilities might explain why a clear association was seen

Table 4. Drug score and number of subjects taking anticonvulsant drugs during pregnancy

	Previous study	Present study
Drug score (range)	0-19.6	0-26.0
Phenytoin	137	65
Phenobarbital	71	20
Primidone	92	19
Carbamazepine	67	55
Valproic acid	27	43
Acetazolamide	15	0
Diazepam	13	5
Methylphenobarbital	13	7
Pheneturide	7	0
Nitrazepam	3	0
Sulthiame	2	2
Ethosuximide	1	1
Clonazepam	0	1
Zonisamide	0	1

Table 5. Comparison of drug scores and number of anticonvulsant drugs between the previous and present studies

	Previous study (%)	Present study (%)	Statistical values
Drug score (mean ± SD)	9.110 ± 7.179	7.126 ± 5.145	$Z = 2.031$ $p = 0.042$
Percentage taking indicated no. of drugs			
0	10.4	1.4	
1	16.1	63.4	
2	27.1	22.1	$Z = 6.512$
3	24.0	10.3	p = near 0
4	16.1	0.7	
5	6.3	2.1	

Z: Wilcoxon rank sum test statistic.
p: Significant propability for Z value.

Table 6. Comparison of the incidence of malformations in previous (1) and present (2) studies after results corrected for five factors significantly different between the two studies

Factor	Study	No. of infants		Mantel-Haenszel test
		Malformed	Not malformed	
Age at delivery (yr)				
<25	1	8	57	
	2	1	38	
≤25-30	1	12	76	$\chi^2 = 4.804$
	2	6	56	$p = 0.028$
≤30	1	6	33	
	2	2	42	
Etiology of epilepsy				
Idiopathic	1	23	148	
	2	9	134	$\chi^2 = 4.620$
Symptomatic	1	3	18	$p = 0.032$
(organic)	2	0	2	
Seizure type				
PGS	1	12	91	
	2	4	58	
SGS	1	4	20	
	2	1	17	
SPS	1	5	17	$\chi^2 = 3.859$
	2	1	7	$p = 0.049$
CPS	1	4	24	
	2	1	34	
Mixed	1	1	14	
	2	2	20	
Drug score				
0	1	2	18	
	2	0	2	
<5	1	3	40	$\chi^2 = 2.554$
	2	3	53	$p = 0.110$
<10	1	4	46	
	2	1	47	
<15	1	7	30	
	2	4	22	
<20	1	6	19	
	2	0	9	
≥20	1	4	13	
	2	1	3	
No. of AEDs				
0	1	2	18	
	2	0	2	$\chi^2 = 1.027$
1	1	2	29	$p = 0.311$
	2	5	87	
2	1	7	45	
	2	1	31	
3	1	6	40	
	2	2	13	
≥4	1	9	34	
	2	1		

1 = previous study.
2 = present study.
PGS = primary generalized seizure.
SGS = secondary generalized seizure.
SPS = simple partial seizure.
CPS = complex partial seizure.
AED = antiepileptic drug.

between methylphenobarbital exposure and the occurrence of malformations in the infants of the subjects in our study. This association must be confirmed, however, with further prospective studies.

Analysis of our data with regard to the possibility of teratogenicity of methylphenobarbital is now in progress. In our present subjects, no relationship appeared to exist between the type of malformations and individual AEDs. However, perhaps this is because of the small number of patients.

Patients in our present study have been treated successfully with a single AED at minimal doses. We changed from polytherapy to monotherapy whenever possible. The changes in AED therapy resulted in a significantly reduced incidence of malformations among offspring. The present data therefore confirm the involvement of AEDs in the production of congenital malformations.

A malformation rate of 6.2% among the infants of our present study subjects is similar to the 5.7% rate among the offspring of non-AED-treated women with epilepsy (derived from nine prospective studies) and near the 4.8% rate among the offspring of the general population (derived from six prospective studies).[23] Similarities between the incidence of malformations in the present study subjects and that in the general population and among offspring of untreated women with epilepsy, together with the failure of putative risk factors other than those related to AEDs to reach a significant level, suggest that AEDs are the primary factors responsible for the increased incidence of malformation in the offspring of women treated with AEDs.

The mechanisms of teratogenicity of AEDs have not yet been clearly established. Some plausible mechanisms have been postulated, however, and considerable evidence for these is accumulating. Most AEDs—particularly valproic acid—cross the placenta, and their active metabolites accumulate in the fetus.[24,25] Dansky et al[26] reported that the incidence of malformations in infants was correlated with maternal levels of phenytoin, and Jäger-Roman et al[7] obtained similar results for valproic acid. The present data suggest that methylphenobarbital has similar effects on the fetus. Animal experiments also showed a correlation between high levels of valproic acid and congenital malformations.[9]

In contrast to the mechanisms discussed above, the teratogenicity of phenytoin was postulated to be the result of the formation of phenytoin epoxides and covalent binding of epoxide—the ultimate teratogen—to constituents of gestational tissues.[27] Strickler et al[28] found a significant correlation between increased cellular toxicity of phenytoin metabolites in vitro and major birth defects in children exposed to phenytoin in utero. Results of the latter report are consistent with the findings of Marts et al,[27] that the inhibition of epoxide hydrolase resulted in an increase in covalent binding of phenytoin metabolites and an increase in the frequency of birth defects in the rat fetus.

Polytherapy increases the metabolic formation of active metabolites of AEDs, such as 4-en-valproic acid,[29] and those of carbamazepine other than 10,11 carbamazepine epoxide.[30] Phenytoin, carbamazepine, and other AEDs are known to be potent inducers of hepatic microsomal oxidation of drugs in humans.[31] The human fetus is equipped with a hepatic monooxygenase system[32] that might catalyze the formation of epoxides[33] and with hepatic and extrahepatic enzymes that metabolize the epoxide.[34] In the human liver, sulfhydryl groups and glutathione that react spontaneously or metabolically with reactive metabolites of drugs also exist.[35] The balance between the enzyme activities that catalyze the formation and the elimination of epoxides could, therefore, be a determinant in the formation of malformations.

Valproic acid also increases the production of epoxide intermediates of carbamazepine by inhibiting epoxide hydrolase.[36] Such data suggest that polytherapy increases the formation of active metabolites, which in turn increase the toxicity of AEDs in humans.[37] Accordingly, combinations of phenytoin, carbamazepine, valproic acid, primidone, and methylphenobarbital increase the teratogenic metabolites. On the other hand, a contribution of genetic factors toward the development of congenital malformations is also suggested. Greenberg et al[13] found a higher incidence of malformations in the families of children with birth defects than in the families of controls. Gaily et al[16] reported that congenital anomalies other than phenytoin-linked hypertelorism and digital hypoplasia[38] were genetically linked to epilepsy. Fraser et al,[14] in contrast, reported that the genotype for epilepsy did not predispose toward the development of congenital malformations. Thus, the role of genetic factors in congenital malformations is still open to discussion.

Other possible factors, such as folate deficiency, have been reported to be causally related to malformations.[10] Hiilesmaa et al[39] failed to observe a significant association between folate levels and congenital malformations, whereas Dansky et al[11] found a significant association and Laurence et al[40] reported that folate supplementation prevented recurrence of neural-tube defects. Reductions in folate levels are caused by AEDs such as phenytoin in a dose-dependent manner,[41] a finding that, again, suggests that AED treatment plays a role in the occurrence of birth malformations. High doses of AEDs and their active metabolites might, therefore, be responsible for an increased incidence of malformations. Our present data certainly support this notion, in that the incidence of congenital malformations was reduced considerably when we switched AED treatment to monotherapy and lowered doses. However, further prospective studies, using larger cohorts, are required to assess the relative contributions of all these factors to the occurrence of congenital malformations in IME.

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